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10/069,840	06/26/2002	Wolf Bertling	10848-021US1	5356

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,840	BERTLING ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

3. For convenience, claim 1, the only independent claim, is reproduced below.

1. (Previously presented) A method for detecting and quantifying first biopolymers (1) that are located in a liquid, where second biopolymers (2) which have a specific affinity to the first biopolymers (1) to be detected are bonded to the surface of a first electrode (E1), and where the first and at least one second electrode (E2) are in contact with the liquid, said method having the following steps:

contacting the liquid with the first electrode (E1),

applying a voltage and/or current across the first electrode (E1) and the second electrode (E2), and

measuring a direct change in the voltage and/or current caused by addition of the first biopolymers (1) onto the second biopolymers (2).

4. For purposes of examination, the claimed method has been interpreted as encompassing the detection of virtually any and all biopolymers, including, but not limited to, catalytic and non-catalytic proteins, antibodies; viral bacterial, plant and animal proteins and glycoproteins, lipoproteins, lipids, rRNA, mRNA, tRNA, single- double- and triple-stranded DNA, as well as polysaccharides, including but not limited to starches and celluloses, and rubber. Further, the claimed method has been interpreted as fairly encompassing the detection and quantification of specific biopolymers when such are present in a mixture of other and potentially competing biopolymers. Said method has also been interpreted as encompassing

5. The specification cites several documents, however, they have not been incorporated by reference and therefore cannot be relied upon for satisfaction of written description, enablement, or best mode requirements.

6. The specification provides but two examples:

a. Example 1, pages 5-6, "Direct-voltage voltammetric measurement;" and

b. Example 2, pages 6-7, "Alternating-current voltammetric measurement."

Neither of thee examples teaches with "such full, clear and exact terms" as fully describe the full scope of the invention. The specification also fails to reasonably suggest that applicant had possession of the invention at the time of filing.

Response to argument

7. At page 7 of the response of 02 February 2004, applicant directs attention to Figs. 1 and 2 as well as Examples 1 and 2 as providing an adequate written description of the invention, noting with particularity that starting material is identified (DNA- HGH1), as well as the applied voltage and measurement methods.

8. The above argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection as the claims encompass biopolymers of virtually any and every type, not just purified HGH1 in a known concentration being used under controlled conditions. Rather, and as noted above, the claimed method fairly encompasses the accurate and reproducible detection and quantitation of a wide variety of biopolymers. The specification is essentially silent as to how these other embodiments are to be practiced.

9. It is noted that Examples 1 and 2 do not teach how to quantitated the results. Applicant, at page 7, second full paragraph, states the change in capacitance "can be used to detect and quantify (first) biopolymers that are complementary to (second) biopolymers bound to the surface of the electrode." There is, however, a significant difference from describing how any and all manner of biopolymers can be both detected and quantitated, and simply asserting that such is possible, as is the case here.

10. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-13 remain rejected under 35 USC 112, first paragraph, and failing to comply with the written description requirement.

11. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

12. As presented above, the specification does not provide an adequate written description of the claimed invention nor does the specification reasonably suggest that applicant had possession of the invention now claimed. It is well settled that one cannot enable that which they do not yet possess. Accordingly, and in the absence of convincing evidence to the contrary, claims 1-13 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

As noted above, the specification provides but two examples, yet neither example discloses performing both detection and quantification. Even if such was disclosed, which they are not, the two examples fail to set forth starting materials and reaction conditions for the extremely diverse genus of biopolymers, which can and do bind one another. Further, the specification is effectively silent s to how one of skill in the art would both detect and quantify biopolymers that vary in base composition or where the sample comprises a highly heterogeneous mixture of biopolymers. While there is no *per se* rule requiring exemplification of manners in which a claimed device is to be used, the level of disclosure provided in order to enable the full scope of the claimed invention is held to be inversely proportional to the predictability of the invention. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

13. The claimed invention clearly relates to matters of chemistry, not only in regards to the biopolymers that are to be detected and quantified, but also in regards to their ability to migrate toward and be immobilized on an electrode. Given that biopolymers such as proteins and nucleic

acids can undergo denaturation and degradation when subjected to electric fields, it is critical that the skilled artisan be provided with guidance as to what field strengths should be applied for different biopolymers, be they nucleic acids, proteins, lipids, or polysaccharides.

The claimed invention clearly relates to matters of chemistry, not only in regards to biopolymers generally but also in regards to hybridization reactions for as seen at page 7 of the disclosure, applicant clearly contemplates having a probe immobilized on an electrode such that hybridization takes place. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

- The purity of the nucleic acid preparation.
- Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
- Length of homologous base sequences- any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
- Ionic strength- the rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.
- Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

- Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.
- Denaturing reagents- the presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.
- Incubation- the longer the incubation time, the more complete will be the hybridization.
- Volume exclusion agents- the presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.
- Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products. The specification, however, is silent as to how these art-recognized difficulties are to be overcome. Rather than set forth a reproducible manner by which the claimed invention is to be made and used, applicants are seemingly trusting in the public to determine how to make and use the invention. Such non-disclosure does not rise to the level of an enabling disclosure. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166

> USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are not enabled by the disclosure.

Response to arguments

At page 5 of the response applicant asserts that the rejection should be withdrawn, noting that the specification teaches, "that the method 'can be carried out simply and quickly' (page 2 lines 34-35)."

The above argument has been fully considered and has not been found persuasive. Simply asserting that a method can be practiced "simply and easily" does not in and of itself satisfy the requirements for full enablement. While agreement is reached in that the specification does provide 2 example and two figures, such disclosure is directed only to the matter of HGH1 DNA under controlled conditions, and even under those conditions, the specification is essentially silent as to how the quantity of DNA is to be determined. Upon review of the examples, applicant knew the amount of DNA added to the solution prior to conducting the assay, not determine the quantity of DNA as a result of the assay.

14. At page 5, penultimate paragraph, applicant attempts to unfairly shift the burden of enablement from applicant to the public by asserting, "those of skill in the art know what field strengths to use in the methods of the invention with different biopolymers. See, for example, page 5, lines 14-21." For convenience, page 5, lines 14-21, is reproduced below.

> The terms first biopolymer and second biopolymer here are taken to mean, in particular, proteins, peptides, DNA, RNA and the like. The first biopolymer can be, in particular, a single-stranded DNA or RNA which is complementary to the second biopolymer. In step b, the change in voltage and/or current caused by the hybridization of the above-mentioned biopolymers is thus preferably measured.

Clearly, the cited (reproduced) passage does not teach with any detail as to how one is to practice the claimed method for any and all manner of biopolymers.

15. At page 6 of the response, applicant asserts that the two examples provided adequately enable the full scope of the claimed method. This argument ahs been fully considered and has not been found persuasive as it fails to address how the non-disclosure of starting materials (e.g.,

proteins, antigens, lipids, glycoproteins, etc.) and reaction conditions does not cause undue experimentation on the part of the public, as noted in *Genentech*.

16. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-13 remain rejected under 35 USC 112, first paragraph, as not complying with the enablement requirement.

Claim Rejections - 35 USC § 102/103

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1-9 and 13 remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 5,871,918 (Thorp et al.).

22. For purpose of examination, the term "biopolymer" has been interpreted as encompassing nucleic acids (DNA, RNA, and modified nucleotides).

23. Thorp et al., column 10, discloses detecting nucleic acids (applicant's biopolymer) through the use of at least two electrodes where one nucleic acid is immobilized to a first electrode and is allowed to come into contact with a solution that comprises a complementary nucleic acid that will form a hybridization complex with the immobilized nucleic acid, or probe.

24. Thorp et al., penultimate paragraph, discloses the electronic signal may be characteristic of any electrochemical method, including cyclic voltammetry, normal pulse voltammetry, chrononmperometry, [and] square-wave voltammetry. Such disclosure is considered to anticipate, or in the alternative, render obvious the claimed methods of measuring the current or voltage.

25. For the above reasons, and in the absence of convincing evidence to the contrary, the claimed invention is anticipated, or rendered obvious, by the prior art of record.

Response to argument

At page 8 of the response, applicant asserts that the rejection is improper and should be withdrawn as it is not necessary to employ redox-active molecules and that the prior art does not teach detecting and quantitating in the absence of redox-active molecules.

The above argument ahs been fully considered and has not been found persuasive for while the claimed method may well encompass embodiments where no redox-active molecules are used, the method does not bar their use. In short, applicant is arguing limitations not present in the claims. Therefore, and in the absence of convincing evidence to the contrary, the rejection is maintained.

Conclusion

26. Rejections and/or objections that appeared in the prior Office action and which were not repeated hereinabove have been withdrawn.

27. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

28. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
15 June 15, 2004